REMARKS

Claim Amendments

Claim 1 is amended to recite, *inter alia*, a "vaccine and an immunostimulatory" amount of a polypeptide. Support for this amendment is found in the specification, *e.g.*, at page 14, lines 29-30, page 7, lines 1-3 and Claim 6 as originally filed.

Claim 6 and Claims 10-45 are canceled.

Claim 7 is amended to change claim dependency in view of canceling Claim 6.

Claim 46 is new. Support for this claim is found in the specification, *e.g.*, at page 11, lines 18-26.

Objection to the Specification

The title of the invention is objected to as being not descriptive. As suggested by the Examiner, Applicants have amended the Title to "HMGB Polypeptides for Increasing Immune Responses".

Rejection of Claims 1-9 Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate with the claims. In particular, the Examiner states that:

> The specification does not teach the genus of HMGB B box polypeptides and functional variants thereof that induce an immune response and treat or prevent cancer or a viral infection (e.g., HIV/AIDS). There are no working examples of a HMGB B box polypeptides or functional variants thereof that induce an immune response and treat or prevent cancer or a viral infection. (Office Action, page 5).

The Examiner further asserts:

> With respect to administration of a pharmaceutical composition comprising an HMGB B box polypeptide further comprising a vaccine and, in turn, preventing cancer in a patient, reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations, which have been successfully pre-screened and are predisposed to particular types of

> cancer. . . . Further, a preventive administration must also assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. (Office Action, page 7).

Applicants respectfully disagree. As an initial matter, Applicants submit that the pending claims are directed to compositions, and not to methods of treatment, such as treating cancer or viral infections. Thus, whether or not Applicants' claimed compositions are enabled in a method for treating patients with cancer, viral infections, or other diseases, should not be at issue in the pending application. Furthermore, whether a "therapeutic will be safe and tolerable for anyone susceptible to the disease" is more properly regulated by the FDA and not a question for patentability (see MPEP § 2107, 8th Ed. Rev. 7).

As stated in the MPEP:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). (MPEP § 2164.01, 8th Ed. Rev. 7).

Several factors are to be considered in determining if any experimentation is undue, including: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. *Id.*

Applicants submit that the quantity of experimentation necessary to make and use Applicants' claimed invention is merely routine for one of skill in the art when guided by

Applicants' specification and what was known in the art at the time of filing. For example, Applicants have fully described and detailed in the specification methods of making and identifying a polypeptide comprising an HMGB B box ,or a functional variant thereof, which do not comprise an HMGB A box (see, *e.g.*, Example 2: Mapping the HMGB1 Domains for Promotion of Cytokine Activity at page 29 *et seq.*, FIG. 1). Thus, Applicants have provided clear guidance to those skilled in the art methods for identifying B box domains in an HMGB polypeptide. Furthermore, Applicants have provided several examples of specific amino acid sequences for HMGB B boxes (see, *e.g.*, page 11, lines 5-6; page 11, line 27 through page 12, line12). Additionally, the specification as filed also provides specific amino acid sequences of functional fragments of HMGB B boxes (see, *e.g.*, page 11, lines 21-26). Notably, the application as filed also describes HMGB B box fragments that do not have functional activity (see page 32, lines 9-11; FIG. 3). Thus, a person of skill in the art could readily make and use a polypeptide or functional fragment thereof as currently claimed since the application teaches a representative number of species of the genus of polypeptides and functional fragments thereof.

In addition, the application as filed provides experimental evidence of the *in vitro* and *in vivo* effects of administering an HMGB B box and a biologically active fragment thereof to cells or mice (see Examples 3, 4 and 5). Of particular note, the Examples detail that HMGB Box polypeptides promote cytokine activity in a *dose-dependent* manner (see, *e.g.*, Examples 3 and 5). As a person of skill in the art will readily appreciate from Applicants' specification, cytokine activity can be stimulated by HMGB B boxes at low doses as well as at higher dosages (see, *e.g.*, Example 3, and FIGS. 2A, 2B and 2C). It will also be appreciated from the specification as filed that lower dosages of HMGB B box polypeptides were not lethal in a mouse model for cytokine toxicity (see Example 5, and Table 1: administration of 0.1 mg/mouse of HMGB B box had a 100% (6/6) survival rate).

To conclude, Applicants have provided structural information about the HMGB B boxes, functional fragments thereof, specific examples of amino acid sequences of such polypeptides, as well as methods of using same. A person of skill in the art can readily identify those polypeptides that are encompassed by Applicants' claimed invention. The specification as filed fully enabled a person of skill in the art to make and use Applicants' claimed invention

commensurate with the breadth of the claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 2, 4 and 5 Under 35 U.S.C. § 102(a)

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 102(a) as being anticipated by Taudte *et al.* (Protein Eng. (2001) 14: 1015-01023; IDS reference C69).

Applicants respectfully disagree. Claim 1, as amended, recites *inter alia*, a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Taudte *et al.* do not describe a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Thus, Claim 1, as amended, and Claims 2, 4 and 5 which are dependent thereon, are novel over Taudte *et al.*

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 2, 4 and 5 Under 35 U.S.C. § 102(b)

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bianchi *et al.* (EMBO J. (1992) 11: 1058-1063; IDS reference C11).

Applicants respectfully disagree. Claim 1, as amended, recites *inter alia*, a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Bianchi *et al.* do not a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Thus, Claim 1, as amended, and Claims 2, 4 and 5 which are dependent thereon, are novel over Bianchi *et al.*

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5 and 7 Under 35 U.S.C. § 102(e)

Claims 1-5 and 7 are rejected under 35 U.S.C. § 102(e) as being anticipated by Tracey *et al.* (US 2003/0144201063; IDS reference A6).

Applicants respectfully disagree. Claim 1, as amended, recites *inter alia*, a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Tracey *et al.* do not describe a composition comprising a vaccine and a therapeutically effective amount of a polypeptide, wherein said polypeptide comprises an HMGB B box or a functional variant thereof and does not comprise an HMGB A box. Thus, Claim 1, as amended, and Claims 2-5 and 7 which are dependent thereon, are novel over Tracey *et al.*

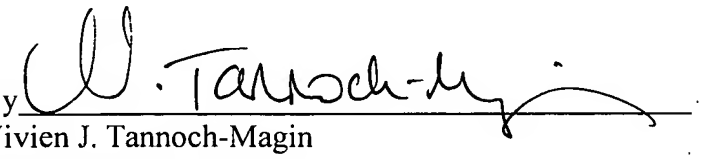
Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

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